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Fabrication of Novel Types of Colloidosome Microcapsules for Drug Delivery Applications

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ABSTRACT

Novel colloidosome microcapsules with aqueous gel cores and shells of different polymeric colloid particles have been prepared and characterized. Our preparation technique involves templating water-in-oil emulsions stabilized by either polymeric microrods or polystyrene (PS) latex particles and subsequent gelling of the aqueous phase with a suitable hydrocolloid. The obtained colloidosome microcapsules were transferred in water after dissolving the oil phase in ethanol and multiple centrifugation/washing cycles with ethanol and water. The presence of an aqueous gel core was found to enhance the structural integrity and mechanical stability of the obtained colloidosomes. In the case of latex particles forming the colloidosome membrane, the effect of the oil type on the final structure of the colloidosome shell was also studied. It was shown that by using appropriate oil, the latex particles within the colloidosome shell can be partially or completely swollen which not only binds them together but also allows direct control over the membrane pore size and its permeability with respect to entrapped species. Such microcapsules can find various applications for development of novel drug and vaccine delivery vehicles, slow release of cosmetic and food supplements.

INTRODUCTION

Colloidosomes are microcapsules with shells consisting of coagulated or partially fused colloid particles[1-5]. It has been recognized that the colloidosome membranes offer a great potential in controlling the release rate of entrapped species. Their major advantage is that the membrane pores size can be varied by varying the size of the particles and by controlling their degree of fusion. Here, we report fabrication of novel colloidosome microcapsules with shells of solid microparticles and aqueous gel cores. Our method mimics the recently developed Gel Trapping Technique[6,7] for trapping particle monolayers at liquid surfaces by gelling the aqueous sub-phase. The basics of this method are illustrated in Figure 1 and involve the following three stages:

(i) Hot aqueous solution of agarose is emulsified in oil in the presence of solid colloid particles to produce particle-stabilized water-in-oil emulsion and then the system is cooled off to set the agarose gel;

(ii) The obtained suspension of aqueous gel microcapsules is diluted with ethanol and centrifuged to separate them from the supernatant;

(iii) The microcapsules are washed with ethanol and water and finally re-dispersed in water.

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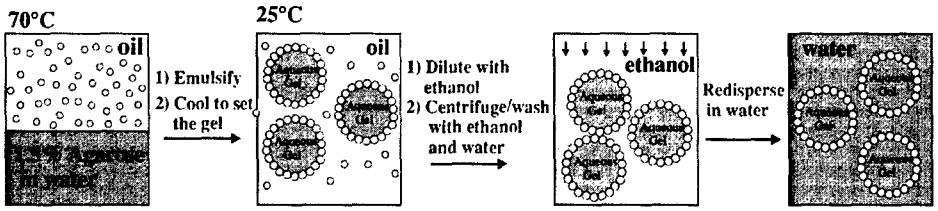

Figure 1: Schematics of our method for preparation of the colloidosomes microcapsules of PS latex particles and aqueous gel cores. Same technique is also used with the polymeric microrods.

Giant colloidosome microcapsules of diameters varying between several tens to several hundreds of micrometers were prepared using this technique. We were able to fabricate colloidosomes of shells composed of two different types of polymeric microparticles: (i) spherical latex micoparticles, functionalized with amine-groups and (ii) SU-8 epoxy microrods. We give the details of the common procedure for preparation of colloidosomes with aqueous gel cores and shells of spherical latexes or polymeric microrods.

EXPERIMENTAL DETAILS

The water-in-oil emulsion templates were stabilized by either (i) 3.9 μm aliphatic amine latex particles (3wt% suspension supplied by Interfacial Dynamics Corp., USA) or (ii) SU-8 epoxy resin microrods (~ 4wt% in ethanol, prepared as described in Ref. 8). The system consisted of an aqueous phase containing 1.5wt% of gelling agent (agarose D5 supplied from Hispanagar, Spain) and either tricaprylin (min 99%, from Sigma) or sunflower oil (Trex, UK) used without further purification as the oil phase. In a typical preparation, 320 μL of an approximately 5 times concentrated polymeric particles suspension were deposited in a polyurethane tube (10 mL capacity) and milliQ water added up to 500 μL. Agarose D5 was then added at 1.5 wt% along with 1.6 wt% of sodium chloride (min 99.9%, from BDH). The aqueous phase was then heated up to over 95 °C with gentle agitation to melt the gel formed. Once the agarose was completely dissolved, the temperature was decreased to 75 °C. Simultaneously, 4.5 mL of oil were heated up to the same temperature and added to the aqueous phase. The system was then emulsified by passing 5 or 6 times in a preheated syringe and needle (0.6 x 25 mm). The emulsion was subsequently left to stir at 75°C for 15 minutes and then cooled down to room temperature to set the agarose gel. Samples of the gelled emulsion template were observed with an optical microscope to check for a nearly complete particle monolayer adsorbed at the interface. In cases where sunflower oil was used (chosen not to induce particle swelling), the emulsion template was treated with glutaraldehyde (70%wt aqueous solution, from Sigma) to cross-link the particle within the monolayer. The function of the glutaraldehyde was to cross-link the amine-groups on the particles surface and to bind them within the shell. For this purpose, 1 mL of glutaraldehyde solution was stirred with 1 mL of sunflower oil for 2 hours. 20 μL of this oil phase saturated with glutaraldehyde was added to the water-in-oil emulsion and the system was stirred for 2 hours before dissolving the oil in ethanol and transferring the colloidosome capsules to water. The stirring is essential to prevent the clumping of the gel beads due to inter-particle bridging with glutaraldehyde.

In both cases of oils used (sunflower oil or tricaprylin), the following strategy was used to transfer the aqueous gel beads encapsulated with the colloid particle monolayer from the oil phase into water. 1 mL of the emulsion was added to 1 mL of ethanol (as both oils used were soluble in ethanol) and then the mixture was centrifuged to separate the microcapsules from the supernatant. The microcapsules were further washed 3 times with ethanol before being transferred in milliQ water. Samples of the obtained microcapsules were then imaged by optical microscopy (Olympus BX-51 fitted with DP50 digital camera).

DISCUSSION

In this section we present (i) the results with colloidosomes produced by using spherical PS latex particles, followed by (ii) the results involving the preparation of microcapsules with shells of SU-8 epoxy microrods.

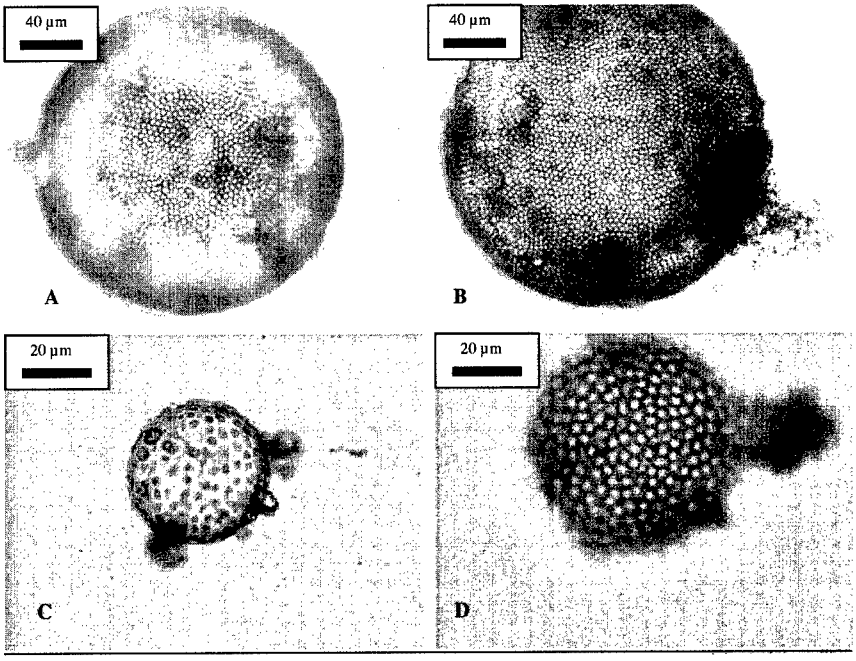

Figure 2: Optical images of colloidosomes with shells of PS particles obtained from the initial sunflower oil-in-water emulsion (A and B) and from the tricaprylin-in-water emulsion. In the latter case, the system was left at 75°C for 12 min (C) and 20 min (D) resulting in a different degree of swelling of the latex particles within the polymeric shell.

In the first series of experiments we used sunflower oil to produce water-in-oil emulsion templates stabilized only by latex microspheres. Then, we used cross-linking with glutaraldehyde to reinforce the particle monolayer around the gelled emulsion drops so that they can sustain their transfer in water. For preparation of colloidosome capsules, the hot emulsion was cooled to room temperature to set the agarose gel and the transfer of the gel beads into water was performed as described in Fig. 1. Fig. 2A shows a typical image of a microcapsule obtained after transfer in water phase. We found that the cross-linking with glutaraldehyde significantly improved the quality of the monolayer retained on the surface of the gel beads.[6] Indeed, one can see from Fig. 2A that the almost perfect monolayer of particles forming the capsule membrane has been preserved throughout the transferring procedure. When we used tricaprylin oil instead of sunflower oil we found that the latex particles undergo rapid swelling when in contact with this oil phase at 75°C. This is well illustrated in Fig. 2C where the capsule shown has acquired a "golf ball" appearance after swelling the particle monolayer forming its shell and has kept its overall structure after its transfer in the water phase.[6]

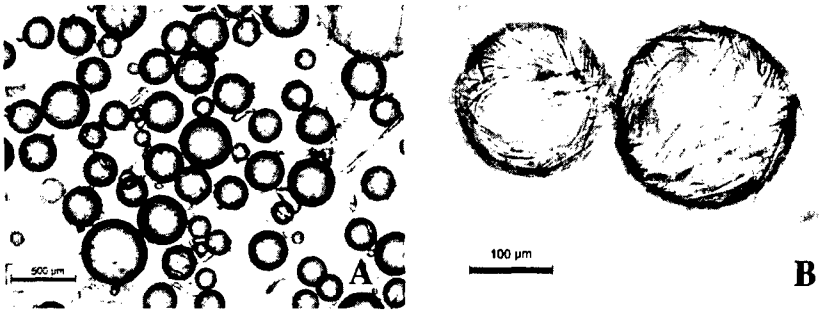

Figure 3: Optical images showing (A) a stable water-in-oil emulsion stabilized only by the polymeric rod-like microparticles and (B) the resulting colloidosomes after transferring the water-in-oil emulsion drops (microcapsules) into the water phase.

We also used polymeric microrods made of SU-8 photoresist[8] as solid stabilizers of the emulsion template. In this case, the water drops in tricaprylin appeared to be fully coated with microrods adsorbed at the oil-water interface (Fig. 3A). Note that, to our knowledge this is the first report of an emulsion stabilized only by rod-like microparticles. In addition, due to the dense layer of adsorbed microrods on the surface of the drops of emulsified hot agarose solution, their coalescence stops completely.[8] The gelled beads were then transferred in water by the technique described above and studied by optical microscopy. The obtained microcapsules in water were recorded as presented in Fig. 3B which shows the 'hairy' colloidosome capsules redispersed in water, after their shells of polymeric microrods have been strengthened by glutaraldehyde cross-linking which proved to be as efficient for this purpose as in the case of latex particles.

CONCLUSIONS

We report a novel technique for preparation of colloidosomes based on aqueous gel core encapsulated with a monolayer of colloid particles. This was achieved by templating water-in-oil emulsions stabilized by spherical latex particles or polymeric microrods followed by gelling the aqueous phase with agarose, dissolution of the oil phase in ethanol and redispersion of the obtained colloidosomes in water. The agarose gel core gives the capsules enough mechanical strength to survive the treatment with ethanol, the centrifugation/washing cycles and the transfer in water, and preserves the structure of the colloidosome membrane. It also provides the advantage of two levels of encapsulation. The first level is provided by the gel network which pore size is determined by the agarose concentration. The second level is given by the colloidosome membrane itself which determines the total out-flux of released component from the capsule. The permeability of the latter membrane can also be controlled by the degree of swelling of the particle in the monolayer constituting the shell in the case of PS latex particles.

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